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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,402	08/01/2003	V. Suzanne Klimberg	781.020US1	6071

21186 7590 02/26/2009

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,402	KLIMBERG ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,10-14,44-53,55 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,10-14,44-53,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 11/26/2008, are acknowledged and entered. Claims 6, 10-14, 44-53, and 55-56 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/26/2008 has been entered.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 6, 10-14, 44-53, and 55-56 as being unpatentable over Willmore *et al.* in view of Shinal *et al.* and Good *et al.* is **withdrawn** in light of Applicant's arguments.

Claims 6, 10-14, 44-53 and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Skubitz *et al.*** (USP No. 5,545,668; Issued Aug. 13, 1996) (cited in IDS filed 4/29/2005) in view of **Shinal *et al.*** (WO 00/69470; Published Nov. 23, 2000) and **Klimberg *et al.*** (Am. J. Surg., 1996, vol. 172, pages 418-424) (cited in IDS filed 11/2/2004).

The instant claims recite a method of protecting normal tissue against damage from radiation therapy comprising orally administering to a mammalian subject afflicted with breast cancer and treated with radiation therapy a composition comprising glutamine and about 20-40 wt.-% carbohydrate.

Skubitz *et al.* disclose a method of treating oropharyngeal mucositis comprising orally administering glutamine at a rate of about 4.5 g/m^2 per day to patients that experience or may develop oropharyngeal mucositis, especially those caused by chemotherapy or radiotherapy (Abstract).

The inventors teach that damage to the oropharyngeal mucosa due to chemotherapy may be greatly decreased by taking glutamine daily at a dosage of between 0.8 to 8 grams per 70 kg and that such doses should also work well to minimize damage due to radiotherapy (col. 4, lines 10-14). Skubitz *et al.* disclose a dose range of glutamine ranging from about 0.01 to about 0.15 grams per kg as a total dose (*i.e.*, about 10 mg/kg to about 150 mg/kg) (col. 7, lines 16-25). These doses of glutamine obviate the doses of glutamine recited in claims 44 and 46-47.

Skubitz *et al.* further teach that the administration of glutamine increases the therapeutic index of chemotherapy and radiotherapy by lessening the associated stomatitis, thus preventing the need to decrease the treatment dose intensity (col. 8, lines 34-40).

With regard to the claimed compositions comprising glutamine and carbohydrate, e.g., one or more monosaccharides or disaccharides (claim 48) such as a sugar alcohol (claim 49), Skubitz *et al.* teach compositions comprising 50 grams L-glutamine, 4 parts ORA-Sweet, 2 parts ORA-Plus, and 2 parts water (col. 4, lines 59-64). This composition contains 500 mg/mL L-glutamine, 30% sucrose, 2.5% glycerin, 2.8% sorbitol, 0.04% citric acid, 0.36% $NaPO_4$, 0.16% cellulose and carboxymethylcellulose, 0.04% carrageenan, and 0.04% xanthum gum (col. 4, line 65 to col. 5, line 2). The reference thus teaches a composition comprising glutamine and 20-40 wt.-% carbohydrate (*i.e.*, sucrose), which is a disaccharide as recited in claim 48 and a sugar alcohol as recited in claim 49.

The compositions disclosed in Skubitz *et al.* do not contain other amino acids other than glutamine, thus teaching the limitations of claims 52-53.

To the extent that Skubitz *et al.* do not explicitly disclose the weight ratios of total carbohydrate to glutamine as recited in claims 50-51, the Examiner relies on Shinal *et al.*, who disclose compositions and methods for increasing the cellular uptake of bioactive agents, including glutamine as instantly claimed (Abstract; page 6, lines 1-11), thus further motivating the combination of glutamine and a carbohydrate as instantly claimed. The invention describes such compositions and methods as solutions or dispersions comprising an aqueous vehicle and an effective amount of a bioactive compound in combination with an amount of carbohydrate effective to reduce absolute solubility of the bioactive agent in the aqueous vehicle so as to achieve increased absorption of the bioactive agent into target cells (page 3, lines 4-11). The compositions and methods described therein are taught to increase the gastrointestinal epithelial cell uptake of the amino acid glutamine by a factor of over 150x (page 5, lines 19-23). Carbohydrates include monosaccharides, disaccharides and sugar alcohols as recited in instant claims 48-49 (page 3, lines 20-29). The ratio of carbohydrate to active agent is taught to be in the range of 1.5:1 to 20:1, preferably 4:1 to 15:1 in the final aqueous solution thus meeting the limitations of claims 50-51. The limitation "about 20-40 wt-% carbohydrate" as recited in claim 6 is taught at page 10, lines 6-33 wherein 20% to 99%, 15-50%, 30-50% and 20-40% carbohydrate carriers are disclosed. A composition comprising no naturally occurring amino acids other than glutamine is disclosed (*id.* at lines 29-33).

Skubitz *et al.* does not explicitly teach oral administration of glutamine and carbohydrate to a patient having *breast cancer* undergoing radiation therapy. Skubitz *et al.* also do not explicitly teach that glutamine has a protective effect on normal tissue, which Applicants define as non-mucosal tissue such as skin or breast tissue (page 4, lines 26-29).

However, Kilmberg *et al.* review the potential benefits of glutamine in the tumor-bearing host receiving radiation or chemotherapy (page 418, "Objective"). In this regard, the authors teach that a large body of evidence *in vivo* suggests that supplemental glutamine not only decreases tumor growth through stimulation of the immune system but when given with radiation or chemotherapy, glutamine protects the host and actually increases the selectivity of therapy for the tumor (page 418, "Results").

Studies in mammals have demonstrated that with glutamine supplementation, the survival of rats subjected to whole abdominal radiation is increased to 100% and the rats have a general increase in well-being (page 419, right column). Another study demonstrated that oral glutamine supplementation decreased chronic radiation injury in rats (*e.g.*, ulcerations, epithelial atypia, serosal thickening, vascular sclerosis, fibrosis, thickening of the intestinal wall, lymph congestion, and ileitis cystica profunda) subjected to radiation therapy (paragraph bridging pages 419 and 420). The authors conclude that provision of glutamine during abdominal or pelvic radiation therapy may accelerate healing of the irradiated bowel, prevent injury, and decrease the long-term complications of radiation enterotherapy (page 420, left column).

Evidence cited by Klimberg *et al.* further suggests that intravenous glutamine increases the content of GSH in liver and has been shown to exert a protective effect against oxidative injury (page 420, left column). In a model using animals implanted with an MCA sarcoma, supplementation with glutamine resulted in significantly increased tumor kill in irradiated rats compared to rats not receiving glutamine supplementation (page 420, paragraph bridging left and right columns).

With respect to breast cancer, tumor growth of MTF-7 breast tumors was decreased by 40% in glutamine-supplemented rats (page 422, right column). The authors conclude that this result suggests that glutamine, when given alone, upregulates GSH, improves NK activity, and suppresses tumor growth possibly through the action of GSH on PGE2 synthesis (paragraph bridging pages 422 and 423).

In human patients, oral glutamine (21 g/day) given throughout a standardized radiotherapy protocol (whole-pelvis irradiation) resulted in significant improvements in histological and morphometric parameters in rectal biopsies, thus suggesting that oral glutamine supplementation has protective effects on normal rectal tissue (page 423, right column).

In conclusion, the authors state that glutamine administration makes tumors cells more sensitive to radiation and chemotherapy while at the same time restoring depressed levels of GSH in normal host tissues, thereby improving the overall well-being and resulting in decreased morbidity and mortality associated with cancer and its treatment (paragraph bridging pages 423 and 424). Thus, glutamine supplementation "effectively increases the therapeutic index of radiation and chemotherapy" (page 424, left column).

In light of the above cited references, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a composition comprising glutamine to breast cancer patients undergoing radiation therapy. While there is no direct connection between oropharygeal mucositis and radiation therapy for breast cancer, the totality of the prior art suggest that glutamine supplementation has beneficial effects in patients undergoing radiation therapy for cancer. Such effects include increasing the effectiveness of radiation therapy as well as preventing injury of normal tissues in patients undergoing radiation therapy. As such, one skilled in the art would have been motivated to administer a composition comprising glutamine to breast cancer patients undergoing radiation therapy and would have been imbued with at least a reasonable expectation that such administration would increase the effectiveness of the radiation therapy as well as protect normal breast tissue from damage from radiation therapy.

With regard to claims 10-12, although the cited prior art does not explicitly suggest the recited effects of glutamine supplementation on breast tissue, the administration of glutamine to breast cancer patients undergoing radiation therapy would be expected to naturally result in the claimed effects (*e.g.*, preventing or lessening increased breast density and preventing or lessening edema) because the same composition suggested by the prior art is being administered to breast cancer patients undergoing radiation therapy as suggested and motivated by the prior art. Accordingly, the *effects* of such administration are a natural result of the administration of glutamine to the claimed patient population.

Applicant's arguments have been carefully considered but they are not persuasive. Although Applicant's arguments are directed to the previous rejection of the claims over Willmore *et al.* in view of Shinal *et al.* and Good *et al.*, the Examiner will address these arguments as they apply to the present rejection.

Firstly, Applicants argue that they have made the paradoxical discovery that normal breast tissue can be protected against damage from radiation therapy by orally administering an aqueous composition comprising glutamine and carbohydrate to a patient afflicted with breast cancer and treated with radiation therapy (Response, page 5). However, in view of the cited prior art, Applicants discovery that normal breast tissue is protected against damage from radiation therapy is not considered by the Examiner to be unexpected because the cited prior art

suggests that glutamine supplementation has a protective effect on normal tissues. Although this protective effect was demonstrated in pelvic tissue exposed to radiation, the skilled artisan would expect that any normal tissue exposed to radiation would be protected from damage induced by radiation.

Secondly, Applicants argue that they have set forth secondary considerations of long-felt need. In this regard, Applicants argue that the painful side effects of radiation therapy to the skin of breast cancer patients are well-known. The Examiner does not dispute this fact. However, Applicant's demonstration that oral glutamine supplementation to breast cancer patients undergoing radiation protects normal breast tissue from damage are not indicative of fulfilling an important, long-felt need when the cited prior art reasonably suggests that oral glutamine supplementation would have this effect. In other words, the cited prior art provides a method for fulfilling the long-felt need of protecting normal breast tissue from damage from radiation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 6, 10-14, 44-53, and 55-56 as being unpatentable over claim 1 of USP No. 7,186,517 in view of Shinal *et al.* (WO 00/69470) and Good *et al.* (U.S. Patent No. 6,666,811) is **withdrawn** in light of Applicant's arguments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614